# Lutetium (177Lu) vipivotide tetraxetan (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

## General information [1]

| Drug description | Indication |
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| The active substance of Pluvicto® is lutetium (177Lu) vipivotide tetraxetan, a therapeutic radiopharmaceutical, which binds to cancer cells expressing the prostate-specific membrane antigen and delivers therapeutic radiation to the targeted cells, causing DNA damage that can lead to their death. | Lutetium (177Lu) vipivotide tetraxetan (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy. |

## Current treatment [2]

- ❖ Drugs recommended by NICE for treating mCRPC after chemotherapy with a docetaxel regimen are cabazitaxel, enzalutamide and abiraterone according to specific criteria listed in the NICE pathway.
- ❖ However, treatment options beyond third-line are currently limited, i.e. in patients treated with taxane-based chemotherapy (including cabazitaxel) and AR-directed therapy (including both enzalutamide, abiraterone).

## Regulatory status

### EMA [1, 3]

**Approval status for this indication**: On 13 October 2022, the CHMP adopted a positive opinion, recommending granting marketing authorisation for **Pluvicto®**.

<u>The full indication is:</u>

- ❖ Pluvicto® in combination with ADT with or without AR pathway inhibition is indicated for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy.

**Other indications**: none

- ✓ **Medicine is under additional monitoring**

On 13 October 2022, the CHMP adopted a positive opinion, recommending granting marketing authorisation for **Locametz®,** intended for the diagnosis of prostate cancer.

<u>The full indication is:</u>

- ❖ **Locametz®**, after radiolabelling with gallium 68, is indicated for the detection of PSM-positive lesions with positron emission tomography in adults with prostate cancer in the following clinical settings:
  - Primary staging of patients with high-risk prostate cancer prior to primary curative therapy.

### FDA [4]

**Approval status for this indication**: On 23 March 2022, the FDA approved **Pluvicto®** (active ingredient lutetium Lu 177 vipivotide tetraxetan) for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy.

**Other indications**: none

On 23 March 2022, the FDA approved **Locametz®** (active ingredient gallium Ga 68 gozetotide), a radioactive diagnostic agent for positron emission tomography of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Locametz® is the first radioactive diagnostic agent approved for patient selection using a radioligand therapeutic agent.

Patients with previously treated mCRPC should be selected for treatment with Pluvicto® using Locametz® or another approved PSMA-11 imaging agent based on PSMA expression in tumours. PSMA-positive mCRPC was defined as having at least one tumour lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded from enrolment if any lesions exceeding certain size criteria in the short axis had uptake less than or equal to uptake in normal liver.

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| • Suspected prostate cancer recurrence in patients with increasing serum prostate-specific antigen levels after primary curative therapy.<br>• Identification of patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. | |

## Costs

Currently, there is no cost information available.

## Posology and method of administration [5]

- **Important safety instruction**
  - Pluvicto® should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings and after evaluation of the patient by a qualified physician.
  - Radiopharmaceuticals, including Pluvicto®, should be used by or under the control of healthcare professionals who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radiopharmaceuticals.
- **Patient identification**
  - Patients should be identified for treatment by PSMA imaging.
- **Posology**
  - The recommended treatment regimen of Pluvicto® is 7 400 MBq IV every 6 weeks (±1 week) for up to 6 doses unless there is disease progression or unacceptable toxicity. Medical castration with a GnRH analogue should be continued during treatment in patients who are not surgically castrated.
- **Treatment monitoring**
  - Laboratory tests should be performed before and during treatment with Pluvicto®. Dosing may need to be modified based on the test results.
  - Haematology (haemoglobin, white blood cell count, absolute neutrophil count, platelet count)
  - Kidney function (serum creatinine, calculated creatinine clearance
  - Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin)

## Warnings and precautions [6]

- **Risk from radiation exposure**
  - Minimise radiation exposure during and after treatment with Pluvicto® consistent with institutional good radiation safety practices and patient treatment procedures.
  - Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.
- **Myelosuppression**
  - Perform complete blood counts.
  - Withhold, reduce dose, or permanently discontinue Pluvicto® and clinically treat based on severity.
- **Renal toxicity**
  - Advise patients to remain well hydrated and to urinate frequently.
  - Perform kidney function laboratory tests.
  - Withhold, reduce dose, or permanently discontinue Pluvicto® based on severity.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise male patients with female partners of reproductive potential to use effective contraception.
- **Infertility**
  - Pluvicto® may cause temporary or permanent infertility.

## Study characteristics [7-11]

| Trial name | *n* | Intervention (I) | Comparator (C) | PE | Characteristics | Biomarker | Funding | Publication(s) |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| VISION NCT03511664 | 831 (2:1) | Standard care[1] + IV infusions of 177Lu-PSMA-617 at a dose of 7.4 GBq (200 mCi) once every 6 weeks for 4 cycles[2] | Standard care alone | Imaging-based PFS + OS (alternate PEs) | **ongoing**[3], prospective, open-label, randomised, international, phase 3 | PSMA | Endocyte, a Novartis company | [10] |

| **Efficacy** (I vs. C) | **Safety** (I vs. C), n=529 vs. 205[4] |
|---|---|
| **Analysis set for imaging-based PFS (n=581):**<br>**Median imaging-based PFS**: 8.7 months vs. 3.4 months; HR for progression or death 0.40; 99.2% CI, 0.29-0.57; p<0.001 (significance level, 0.008)<br>**Median OS:** 14.6 months vs. 10.4 months; HR for death, 0.63; 95% CI, 0.51-0.79<br>**Patients who received post protocol taxane**: 18.6%<br>**Patients who received post protocol platinum-containing therapy**: 6.9%<br>**Median time to the first symptomatic skeletal event or death**: 11.5 months vs. 6.8 months, HR 0.50; 95% CI, 0.40-0.62; p<0.001 (significance level, 0.05)<br>**Complete response** among the 248 patients who had measurable disease at baseline: 9.2% vs. 0<br>**Partial response** among the 248 patients who had measurable disease at baseline: 41.8% vs. 3.1%<br><br>**All patients who underwent randomisation (n=831)**<br>**Median OS**: 15.3 months vs. 11.3 months; HR for death, 0.62; 95% CI, 0.52-0.74; p<0.001 (significance level, 0.05)<br>**Median follow-up:** 20.3 months (95% CI,19.8-21.0) vs. 19.8 months (95% CI, 18.3-20.8) in the control group<br><br>**Health-related quality of life (HRQoL), pain and safety outcomes**:<br>❖ Other secondary endpoints included safety and patient-reported HRQoL (Functional Assessment of Cancer Therapy Prostate) and pain (Brief Pain Inventory - Short Form).<br>❖ Pre-specified analyses included time to the first occurrence of HRQoL/pain worsening, disease progression or death.<br>❖ Ad hoc analyses included time to worsening only (non-inferential).<br>❖ HRQoL was assessed in the pre-specified rPFS analysis set comprising 581 of the 831 randomised patients. | **AEs of grade ≥3**: 52.7% vs. 38.0%<br>**AEs of all grades that led to discontinuation of 177Lu-PSMA-617**: 11.9 vs. NA<br>**AEs of grade ≥3 that led to discontinuation of 177Lu-PSMA-617**: 7.0 vs. NA<br>**AEs that led to death[5]:** 3.9% vs. 2.9% (all grades); 3.6% vs. 2.9% (grade ≥3) |

[1] Standard-care therapy that was permitted by the trial protocol had to be agreed on and assigned by the physician–investigator before randomisation, but it could be modified at the discretion of the treating physician. Standard-care therapies could **not include** cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib). These constraints were used because of a lack of safety data on combining the investigational drug with these agents. **Permitted treatments** included but were not restricted to the approved hormonal treatments (including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoid at any dose. Castrate testosterone levels had to be maintained throughout the trial.

[2] 2 additional cycles (up to 6 cycles in total) could be administered, at the discretion of the treating physician, in patients who had evidence of response.

[3] The VISION trial is currently ongoing; estimated study completion date is 11/2023.

[4] Data for all the patients who underwent randomisation and received at least one dose of their assigned treatment.

[5] 5 AEs that led to death in the 177Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (n=2), bone marrow failure (n=1), subdural hematoma (n=1), and intracranial haemorrhage (n=1).

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| ❖ HRQoL and pain time-to-worsening analyses favoured the 177Lu-PSMA-617 arm, despite a higher incidence of grade ≥ 3 AEs versus standard of care alone.<br>❖ No new or unexpected safety concerns were noted, including changes in creatinine clearance. | |

**ESMO-MCBS version 1.1 [13]**

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Original | NC | 2A | ≤12 months | OS: + 4.0 months | 0.62 (0.52-0.74) | HR ≤0.65 AND gain ≥3 months | 4 | - | - | - | 4 |
| Adapted | NC | 2A | ≤12 months | OS: + 4.0 months | 0.62 (0.52-0.74) | HR ≤0.65 AND gain ≥3 months | 4 | + 14.7 AEs grade ≥3 | - | -1 | 3 |

**Risk of bias (RCT) [14]**

| Adequate generation of randomisation sequence | Adequate allocation concealment | Blinding | Selective outcome reporting unlikely | Other aspects which increase the risk of bias | **Risk of bias** |
|---|---|---|---|---|---|
| yes | - | no, open-label | unclear[6] | yes[7] | unclear |

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Abbreviations: $^{177}$Lu=Lutetium-177, ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, AR=androgen receptor, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTCAE= Common Terminology Criteria for Adverse Events, DNA=deoxyribonucleic acid, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GBq=Gigabecquerel, GnRH=gonadotropin-releasing hormone, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, Int.=intention, mCi=millicurie, mCRPC=metastatic castration-resistant prostate cancer, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PSMA=prostate-specific membrane antigen, QoL=quality of life, SAE=serious adverse event, SD=standard deviation, ST=standard treatment

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[6] The VISION trial is currently ongoing.

[7] The trial was designed, interpreted, and reported as a collaboration between the lead investigators and employees of Endocyte (the sponsor) and Advanced Accelerator Applications, both of which are Novartis companies. Data were analysed by the sponsor and provided confidentially to the authors. Four authors who are employees of Novartis vouch for the accuracy and completeness of the data. Medical writing and editing assistance was funded by Advanced Accelerator Applications.

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